

## **REMARKS**

Claims 1-3, 5-8, 11, 25, 26, 29, 31-34, 37, 39, and 40 are pending in the application. Claims 1-8, 11, 25, 26, 29, 31-34, 37, 39, and 40 have been rejected. Reconsideration and withdrawal of the rejections set forth in the Office Action dated October 21, 2003 are respectfully requested. The applicant petitions the Commissioner for a three-month extension of time. A separate petition accompanies this amendment.

### **I. Amendments**

Claim 3 is amended to include the features of claim 4. Claim 4 is canceled accordingly.

Claims 5 and 6 are amended for grammatical correction.

Claim 25 is amended to recite dependency from claim 3, rather than claim 4 which stands canceled.

### **II. Rejections under 35 U.S.C. §102**

Claim 3 is rejected under 35 U.S.C. 102(b) as allegedly anticipated by Dixit (U.S. Patent No. 6,159,712). This rejection is respectfully traversed for the following reasons.

#### **A. Summary of Present Invention**

The present invention, as set forth in claim 3, relates to a human cell line for use in producing one or more cytokines. The cell line is prepared by the process comprising:

- (i) obtaining a parental human cell line capable of producing one or more cytokines;
- (ii) modifying the cells by introducing an expression vector comprising the coding sequence for CrmA operably linked to a first promoter, and additional control elements necessary for expression in human cells, into the cells of said cell line;
- (iii) screening and selecting for CrmA-expressing cells; and

- (iv) treating the CrmA-expressing cells in a manner effective to result in enhanced cytokine production, wherein the modified and treated cell line is characterized by a level of cytokine production that is at least two times (2X) the level of cytokine production by the corresponding not-modified parental cell line.

B. The Cited Document

Dixit describes a method for preventing or inhibiting apoptosis in a cell. The method includes introducing into the cell a nucleic acid coding for crmA or for a gene product having crmA activity.

C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131.

The presently claimed cell line is prepared by a process that includes the step of "(iv) treating the CrmA-expressing cells in a manner effective to result in enhanced cytokine production, wherein the modified and treated cell line is characterized by a level of cytokine production that is at least two times (2X) the level of cytokine production by the corresponding not-modified parental cell line."

Dixit nowhere teaches treating a CrmA-expressing cell line to achieve enhanced cytokine production. Dixit is concerned with preventing lymphocyte death and maintaining T cell viability in patients infected with HIV (Col. 9, lines 23-42). Nowhere does Dixit show or suggest additionally treating cells modified to express CrmA in a way to enhance cytokine production.

Accordingly, the standard of strict identity has not been met, and withdrawal of the rejection under 35 U.S.C. §102 is respectfully requested.

III. Rejections under 35 U.S.C. §103

Claims 1-8, 11, 12 [sic], 25, 26, 29-34 [sic], and 37-40 [sic] are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Dixit (U.S. Patent No. 6,159,712), Lau et

*al.*, (U.S. Patent No. 6,159,712) and Suzuki *et al.* (Derwent Abstract XP-002170158). This rejection is respectfully traversed for the following reasons.

First, however, Applicants clarify that claims 12, 30, 38 were canceled in the amendment submitted July 28, 2003. The listing of claims in the paragraph above, without considering the cancellation of claim 3 by the instant amendment, should properly read 1-8, 11, 25, 26, 29, 31-34, 37, 39, and 40.

A. Summary of the Present Invention

The present invention, as set forth in claim 1, relates to a human cell composition for use in producing one or more cytokines. The cell line is characterized by expression of the coding sequence for an anti-apoptotic protein and a level of cytokine production that is at least two times (2X) the level of cytokine production exhibited by a corresponding parental cell line that does not express the coding sequence for the anti-apoptotic protein.

The invention also relates to human cell line prepared by a particular process, as embodied in claim 3 and summarized above.

B. The Prior Art

DIXIT is described above.

LAU ET AL. describe a method to increase production of interferon in a cell by modifying the cell to overproduce dsRNA dependent kinase (DSRNA-PKR or PKR).

SUZUKI ET AL. describe a method of improving production of a useful target material, such as an antibody, a cytokine, etc., from a cell by inhibiting apoptosis of the cell. Apoptosis is inhibited by introducing into the cell an apoptosis inhibitor gene, such as CrmA, Bcl-2, BAG-1, etc.

C. Analysis

According to M.P.E.P. § 2143, three basic criteria must be met to establish a case of obviousness. "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. Second, there

must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. § 2143.

It is Applicants' position that the first criterion required to establish a case of obviousness has not been met. Specifically, there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings.

The present invention relates to a human cell line having an enhanced level of cytokine production that is at least two times the level of cytokine production exhibited by a corresponding parental cell line. As noted in the specification, and supported in the scientific literature, cells having an enhanced level of some cytokines alone or in combination are often apoptotic, possibly due to up-regulation of the Fas receptor. (See, for example, enclosed abstracts of Yasuoka, Y. et al., *Exp. Cell Res.*, 271(2):214 (2001) finding that combination of  $TNF\alpha$  and  $IFN\alpha$  induce apoptotic cell death; Shin, E.C., et al., *Int. J. Cancer*, 93(2):262 (2001) reporting that  $IFN\gamma$  induces cell death via apoptosis; Lafleur, E.A., et al., *Cancer Res.*, 61(10):4066 (2001) reporting that IL-12 up-regulates Fas expression leading to apoptosis; See enclosed papers of Ling, Z. et al., *Diabetes*, 52:2497 (2003) finding that IL-1 $\beta$  and  $TNF\alpha$  exert distinct apoptotic effect; Chung, I., et al., *Blood*, 101:1324 (2003) reporting that  $IFN\gamma$  upregulates Fas receptor leading to apoptosis; See specification page 4, lines 35-39 reporting that expression of PKR, which enhances cytokine production, triggers apoptosis and cites of Yeung, M.C., et al., *Proc Natl Acad Sci USA* 93:12451-12455 (1996) and Donze, O., et al., *Virol* 256:322-329 (1999) previously submitted with Form 1449 IDS.)

The Examiner argues that it would have been obvious to one of ordinary skill in the art to combine the anti-apoptotic protein crmA of Dixit with the PKR cell line of Lau et al. to arrive at the combination of an apoptosis-suppressive gene for production of cytokines, as suggested by Suzuki et al.

Starting from the teaching of Dixit, a skilled person is taught that apoptosis is prevented or inhibited by introducing into a cell a gene encoding for crmA polypeptide. To arrive at the present invention, one must add to the teaching of Dixit the concept of enhancing cytokine production in a cell. As the Examiner notes (Office action page 7),

enhancing cytokine production in a cell. As the Examiner notes (Office action page 7), and as indicated above, cytokine production is well documented as inducing apoptosis. Because Dixit is concerned solely with preventing or inhibiting apoptosis, there is simply no motivation to combine the teaching of Lau *et al.* of enhancing cytokine production to the teaching in Dixit. In fact, to modify the teaching of Dixit to include the idea of enhancing cytokine production is contrary to the express purpose of Dixit of inhibiting apoptosis, since enhanced cytokine production induces apoptosis.

The teaching of Suzuki *et al.* does not supply the necessary motivation to make the combination of Dixit and Lau *et al.* Suzuki *et al.* are concerned with inhibiting apoptosis to extend the life of a cell that produces a useful material. Like Dixit, Suzuki *et al.* want to extend cell life to prolong production of cellular material by the cell. Suzuki *et al.* nowhere mention cells having an enhanced cytokine production and it would not be obvious to enhance cytokine production in the cells of Suzuki *et al.* for the same reasons it is not obvious to enhance cytokine production in the cells of Dixit, since both teachings are concerned with inhibiting apoptosis. Enhancing cytokine production induces apoptosis, contrary to the intent of Suzuki *et al.*

Starting from the teaching of Lau *et al.*, a skilled person is taught that cytokine production in cells can be enhanced by introducing PKR, a cytokine inducer, into the cells. The teaching of Lau *et al.* is quite clear that production of cytokines is enhanced when cells are manipulated to express PKR, and nothing in the teaching suggests that cell life is too short to achieve this desired goal. Lau *et al.* nowhere mention problems with cell apoptosis or shortened cell life. Thus, there is no motivation from the disclosure of Lau *et al.* to modify the cell life according to the teachings of Dixit or Suzuki *et al.*

The teachings of Dixit and Suzuki *et al.* do not supply the requisite motivation to combine, since (1) Dixit is concerned with an entirely different problem – inhibiting apoptosis to maintain T cell viability - and (2) Suzuki *et al.* are concerned with production of useful matter from the selected cell and nowhere contemplate an additional manipulation to arrive at enhanced production of useful matter.

The requirement of "motivation" or "suggestion" to combine is a safeguard against the use of hindsight combinations. There is no reason one of ordinary skill in the art would have been motivated to select the references cited and combine them to

render the claimed invention obvious, in the absence of the applicant's own teaching as a blueprint.

Accordingly, withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

IV. Conclusion

It is respectfully submitted that each of the pending claims 1-3, 5-8, 11, 25, 26, 29, 31-34, 37, 39, and 40 are in condition for allowance. A Notice of Allowance is respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4402.

Respectfully submitted,

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